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In vitro HIV-1 infection of human uterine mucosa during pregnancy

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Background

During the first trimester of pregnancy, Natural Killer cells represent the main leukocyte population (70%) in the human decidua (maternal uterine mucosa during pregnancy). These decidual NK cells (dNK) have a distinct phenotype from their peripheral blood counterpart. Decidual leukocyte populations contain also antigen-presenting cells (dAPC) like dendritic cells and macrophages, as well as regulatory and gamma-delta T cells.

In vitro, peripheral NK cells inhibit HIV-1 replication by the release of chemokines or cytolytic activity. Furthermore, HIV-1 infected cells, through their altered-ligands-expression, are able to trigger NK cell activation. As an upregulation of NK cell activation has been reported in exposed-non-infected individuals, we thus hypothesized that dNK could play a role in the control of HIV-1 *in utero* transmission by interacting with infected dAPC at the materno-fetal interface.

Materials and methods

Deciduas were obtained from HIV-1 negative women undergoing elective abortions between 6-10 weeks of pregnancy. dNK cells and dAPC were isolated respectively by negative and positive selection using Miltenyi microbeads after collagenase digestion of the tissue. Cell subpopulations were checked for purity and characterized by FACS analysis using specific monoclonal antibodies. Infections were performed *in vitro* with HIV-1 primary isolates, HIV-1 strains carrying a GFP reporter gene or HIV-1 pseudotypes bearing a luciferase reporter gene. Decidual histocultures were also performed and infected with the same strain viruses.

Results

Phenotype of dNK was $CD3^{-}/CD16^{-}/CD56^{high}$ (up to 90%) and they expressed the activation markers CD69 (100%) and NKp44 (40%). Most of dNK expressed the inhibitory receptor CD94/NKG2A but they expressed activating receptors including NKp46, NKp30, NKG2D and CD94/NKG2C. The phenotypes of the main dAPC subpopulations were $CD14^{+}/HLA\text{-}DR^{++}/CD123^{+/-}$ and a few percentages were $HLADR^{++}/CD83^{low}$.

dNK cells were not permissive to HIV-1 infection *in vitro*, even when they were pre-activated with IL-2. In contrast, dAPC subpopulations as well as decidual histocultures were susceptible to R5 and X4R5 HIV strains but not to X4 strains.

Conclusions

In decidual tissue, NK cells have a phenotype of activated cells that might indicate their interaction with dAPC. The infection of dAPC subpopulations by HIV-1 that we observed *in vitro* might impact the cross-talk between dAPC and dNK, especially through receptor and soluble factor expression modifications. It is thus important to further study the consequences of HIV-1 infection on dNK

and dAPC interactions to gain new insights into the role of these immune cells in controlling HIV-1 infection at the materno-fetal interface.